Assessment of Cerebral Blood Flow and Oxygen Metabolism in Human - Validation of Techniques and Preliminary Results

IV. 1 Assessment of Cerebral Blood Flow and Oxygen Metabolism in Human —— Validation of Techniques and Preliminary Results

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INTRODUCTION

Functional level of organs can be assessed in vivo using positron emission tomograph (PET or ECAT) and labelled radio-pharmaceuticals. Substrates like glucose are carried via blood vessels to tissues and it is well known that blood flow is normally adjusted to the rate of tissue metabolism.[1] Discrepancy between flow and metabolism may be seen in some deteriorated conditions like infarct brain[2] or tumour tissues.[3] Therefore measurement of both blood flow and tissue metabolism is useful to evaluate activity or condition of tissues.

We started in the last April to measure regional cerebral blood flow (rCBF), oxygen extraction fraction (rOFF) and oxygen consumption ($rCMRO_2$) applying 15-O steady-state method developed by Jones et al.[4] This article describes accuracy and error assessment of the technique and results of some stimulation studies.

PRINCIPLES

rCBF measurement

15-O labelled CO_2 is inhaled by subjects at constant level. 15-O is transferred from $C^{15}O_2$ to $H_2{}^{15}O$ by carbonic anhydrase in the lung then transported to the brain via blood flow. Amount of radioactivity accumulates in the tissue directly correlates to CBF. According to the Fick's principle changes in the brain per unit time is difference between inflow of the isotope through blood flow and tissue wash-out of the activity via veins as well as physical decay of the radioisotope (λ = 0.341/min) and is written as follows[5]:

$$\Delta Ct = F \cdot Ca^c \cdot Cf \cdot E^c / V - (Ct^c \cdot \lambda + Ct^c / V \cdot F) \qquad (1)$$

where F is flow per V volume of the brain, Ca^c, Ct^c are arterial and tissue concentration of $H_2{}^{15}O$ respectively, Cf is calibration factor between well counter and ECAT and E^c is extraction ratio of $H_2{}^{15}O$ in the tissue (Fig. 1). At equilibrium changes in the brain activity is null and H_2O extraction in the tissue is almost 100 % then

$$rCBF = F/V = \lambda/(Ca^c \cdot Cf/Ct^c - 1) \quad (2)$$

<u>$rCMRO_2$ measurement</u>

15-0 labelled O_2 inhaled produces oxy-hemoglobin in the lung and transferred to the brain where ^{15}O is converted to $H_2{}^{15}O$ through electron transport system in mitochondria. At equilibrium input via blood flow is again equal to the output through physical decay of the isotope and washout:

$$F \cdot Ca^o \cdot Cf \cdot E^o/V = Ct^o \cdot \lambda + Ct^o/V \cdot F - F \cdot Ca^h \cdot Cf/V \quad (3)$$

where E^o is oxygen extraction fraction (OEF) and Ca^o, Ct^o, Ca^h are arterial and tissue concentration of $^{15}O_2$ and arterial concentration of recirculating $H_2{}^{15}O$ respectively. Solving equation (1) and (3) rOEF is calculated. Regional oxygen consumption is then calculated using arterial oxygen content, Ao:

$$rCMRO_2 = rCBF * rOEF * Ao$$

Oxygen extraction and consumption calculated above are much affected by regional blood volume (rCBV), i.e. the values are always over-estimated in the region with increased blood volume. Then ^{11}CO gas study is needed for CBV evaluation. Simplified gas study principles are summarized in Table 1.

METHODS

Bombarding nitrogen gas with 18 MeV deutron, oxygen-15 is produced and transported continuously to the ECAT room. After checking its purity the gas is introduced to patients' face mask at constant level between 8-12 mCi/min for $C^{15}O_2$ study and 12-18 mCi/min for $^{15}O_2$ study. From six to eight minutes inhalation is usually enough to get to equilibrium in brain count and then ECAT scan is started. Arterial blood samples are taken by femoral artery punctures in the early studies or through a radial artery canula. Regional CBF, OEF and $CMRO_2$ are calculated by solving above equations at pixel level. The resolution of the machine is 18 mm at FWHM both axial and trans-axial direction.

Eight normal subjects, 6 men and 2 women, are studied for the analysis. Among them one is left-handed. The mean age of them is 44±11 y.o. between 25 to 58 y.o.

RESULTS

(1) Assessment of the technical errors

Fig. 2 shows data of gas radioactivity transported and total brain count during a scan of a typical case. Fluctuations of radioactivities according to time seem permissible. Radioactive decay of a blood sample are plotted in Fig. 3. The curve has two component, the half life of the fast one is 2 min and of slow one is 20 minutes which corresponds contaminated 11-CO_2. The contamination in the early case is calculated to be 0.005 % (left figure) and in the late one after increasing thickness of the target is 0.001 % (right figure of Fig. 3).

Blood samples are taken in the middle of each scan. Fluctuations of blood count (cpm/g, decay corrected) is analysed in table 2. The mean standard deviation of the fluctuation is 5 to 7 %.

(2) Normal values

Normal values for the three parameter measured in the temporal lobe near insula at OM + 40 to 60 mm planes are shown in Table 3. The mean values in the temporal grey matter near insula are 49 ml/100 g/min, 3.9 ml/100g/min, 0.39 for rCBF, $rCMRO_2$ and rOEF respectively and difference between right and left hemisphere is not obvious (left/right ratio is 0.9 in rCBF). The anterior posterior ratio in rCBF of grey matter is 0.95 ± 0.25 ranging from 0.68 to 1.40. A typical functional images are shown in Fig. 4.

(3) Activation study

Fig. 5 shows effects of hearing stimulation. The subject inhaled $C^{15}O_2$ continuously for about 35 minutes while CBF studies are done before and within vocal music stimulation. Activation of left temporal lobe corresponding hering center is obvious.

DISCUSSION

Positron tomographs in state-of-art are not so suitable to follow rapid wash-out of radioisotopes in tissues that the method to measure blood flow using continuous inhalation of 15-0 labelled CO_2 and O_2 was developed.[4] It has advantages of being possible to measure both flow and oxygen consumption.

Error factors including simplifications of the model are evaluated by Lammertsma et al. (6). In this paper we only discuss technical factors that affect the reproducibility of the results.

(1) Break down of the steady-state

The steady-state requires constant input of radioactive gases to patients and unchanging brain condition from start of inhalation to the end of examination. Radioactive gas transportation is usually constant as long as cyclotron operates without any failure. But brain radioactivity sometimes fluctuate probably due to unstable respiration which may reflect anxiety of patients. We use anesthetic gas mask to pass strict radioisotope regulations. This may give stress to some patients.

(2) Blood count measurement

Because of short-half life of 15-0, the error in time for decay correction of blood count is crucial. According to Lammertsma's simulation[6] permissible time error for decay correction is about 5 seconds in order to keep error level of calculated CBF less than 3 %. We first considered 99.5 % purity of 15-0 gas and less than 0.5 % contamination of $^{11}CO_2$ is enough. It does not affect much on the brain count; actually it just decreases decay constant of 15-0 but not significantly. But because blood is counted usually around 8 minutes after withdrawance from vessel, a little contamination of 11-C significantly increases blood 15-0 count. For example on the condition that blood radioactivity contains 0.5 % or 1.0 % 11-C and is counted at 8 minutes after arterial sampling, decay corrected blood count shall be overestimated 5 or 11 % of true value respectively. Then calculated corticl CBF values may underestimate 15 to 20 % respectively.[6] We modified the target later and 11-C contamination reduced to 0.1 % (Fig. 3).

Fluctuation of blood count of the same subjects analysed in Table 2. The average s.d. of the change is 5.5 % for $C^{15}O_2$ study and simulation shows the value may result 15 % error in cortical CBF. The actual mean CBF value obtained from normals is 49±8 ml/100g/min. The percent s.d. is 16 % and almost same as predicted.

(3) Results of human studies

Because of contamination of grey and white matter true grey value is difficult to be obtained. We selected temporal pole-insular complex as the region of grey matter. Normal values are calculated as 49 ml/100g/min, 3.9 ml/100g/min and 0.39 for rCBF, $rCMRO_2$ and rOEF respectively. The values are quite agreeable in rCBF with those reported for the English but slightly higher in $rCMRO_2$ and rOEF.

Short life of 15-0 is suitable for repeated studies. The time needed to get to reequilibrium in the stimulated brain region is not clear so that the method is so far useful to see stimulated pattern in the brain qualitatively.

References

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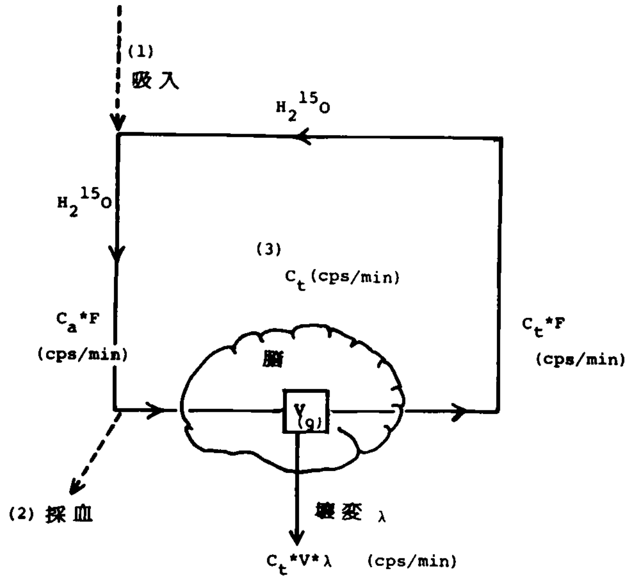
$C^{15}O_2$持続吸入法原理（3）

Fig. 1.



$$C_a*F = C_t*F + C_t*V*\lambda$$

$$CBF = F/V = C_t*\lambda / (C_a - C_t)$$
$$= \lambda / (C_a/C_t - 1)$$

Table 1. Flow chart of gas study principle

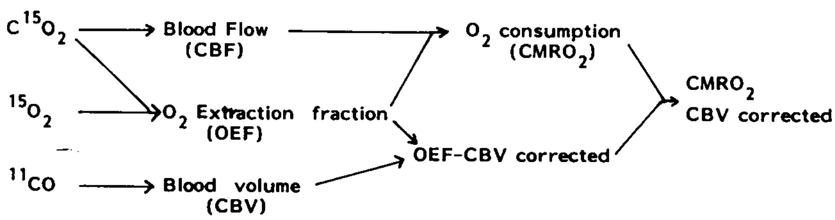


Fig. 2.

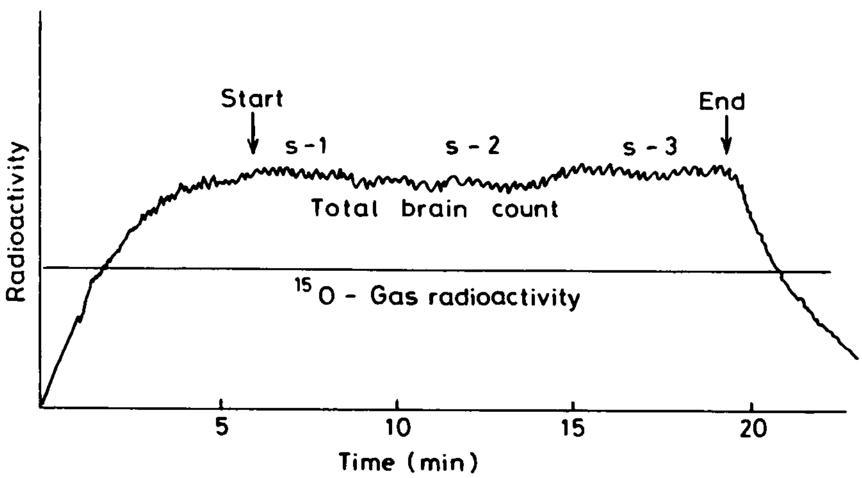


Fig. 3.

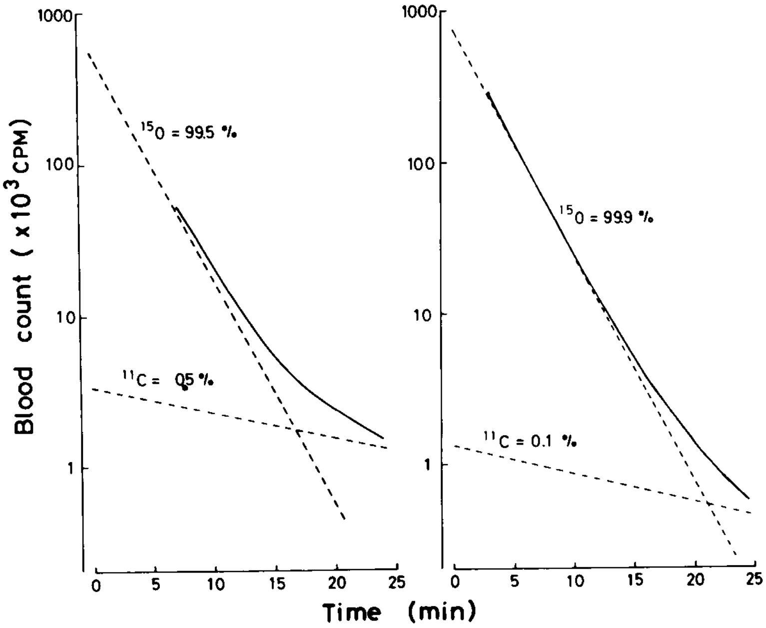


Table 2.

I D	$C^{15}O_2$ study		$^{15}O_2$ study	
	mean	%SD	mean	%SD
55	11670	7.4	13374	9.6
59	18709	5.0	7779	10.0
61	16800	1.8	9488	2.8
71	22778	4.0	20723	5.3
75	14331	8.3	14341	5.3
mean	——	5.3 (±2.6)	——	6.6 (±3.1)

Table 3.

		CBF	$CMRO_2$	OEF
Grey	RT	50±9	3.9±0.5	0.39±0.06
	LT	47±7	3.8±0.5	0.39±0.05
White	RT	22±5	1.8±0.3	0.39±0.06
	LT	22±3	1.7±0.4	0.39±0.06

n=8

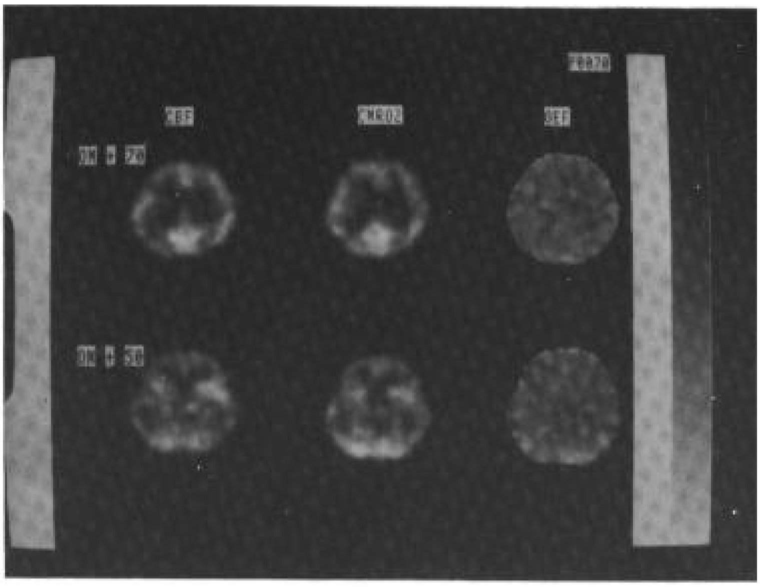

CBF
CMRO2
OEF

Fig. 4.

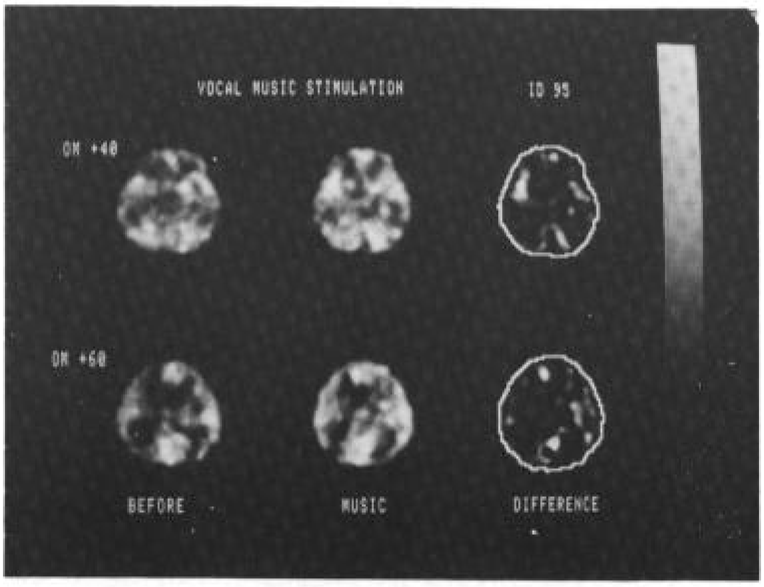

VOCAL MUSIC STIMULATION
ID 95
OM +40
OM +60
BEFORE
MUSIC
DIFFERENCE

Fig. 5.